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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/903,377	07/10/2001	Keith D. Allen	R-365	8328

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1031 Bing Street
San Carlos, CA 94070

EXAMINER

TON, THAIAN N

ART UNIT	PAPER NUMBER
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1632

DATE MAILED: 10/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/903,377	Applicant(s) ALLEN, KEITH D.	
	Examiner Thaian N. Ton	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 July 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-7, 11-16 and 23-39 is/are pending in the application.
- 4a) Of the above claim(s) 1-7, 11-16 and 23-30 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 31-39 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 10 July 2001 and 24 July 2002 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner. Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a). Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Note that the Examiner of Record has changed and is now Thaian N. Ton of Art Unit 1632.

Applicants' Amendment, filed 7/26/04, has been entered. Claim 38 has been amended. Claims 1-7, 11-16, 23-39 are pending. Claims 1-7, 11-16, 23-30 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 2/10/03, Paper No. 11. Claims 31-39 are under current examination.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The prior rejection of claims 31-39 under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

Applicants argue that the prior rejection has been overcome because Applicants argue that the specification provides a correlation between any chemokine receptor 9A-related disease or disorder and the phenotypes exhibited by the claimed mouse. Applicants argue that the assertion of such a correlation is not necessary for the establishment of utility and for the patentability of the claimed

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transgenic mice. Particularly, Applicants argue that specification asserts several potential uses for the transgenic knockout mice, and such uses are well-accepted in the art. For example, the specification teaches method which specifically relate to using the mice to discover, examine and/or develop potential treatments, which may include therapeutic agents, capable of modulating the phenotype of the mice, and in particular, capable of modulating or ameliorating the decreased or impaired agility, coordination or balance exhibited by the mice. See pp. 4-5 of Applicants' Response.

This is not persuasive. In particular, the instant specification fails to adequately demonstrate or teach that the response of the claimed transgenic mouse on the accelerating rotarod is due decreased agility, coordination or balance, and particularly, that this decrease in agility/coordination/balance is due to knocking out the chemokine receptor 9A gene, and that this phenotype is not due to some other physiological or neurological disorder. For example, perhaps the mice have an inner ear disorder or have slower neurological responses. As such, one would not know how to use a compound identified as modulating the phenotype of the claimed knockout, because one of skill would not know what the compound is affecting. Better characterization of chemokine receptor 9A function that correlates chemokine receptor 9A to pain sensitivity, a link between the chemokine receptor 9A gene and a disease or condition, and further testing more definitively correlating the gene disruption specifically to decrease in agility or coordination/balance *per se*, would all provide a stronger correlation between

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disruption of chemokine receptor 9A and decrease in agility/coordination/balance, allowing for credible and specific utility of the claimed mouse. Applicant asserts the utility of the mouse is substantial; however, additional experimentation would be required to determine the usefulness of the claimed mice because it must be determined whether a compound that ameliorates the agility/coordination/balance exhibited by the mice in the rotarod test is agility or coordination or balance, and not some other unidentified characteristic of the mouse that affects its performance in the rotarod test as set forth above.

Applicants argue that the instant specification satisfies the utility requirements set forth in 35 U.S.C. §101 because it has demonstrated a disruption of the chemokine receptor 9A sequence, as described in SEQ ID NO: 1 in a mouse, results in a phenotype specific to that mouse, which is impaired agility, coordination and balance when compared to wild-type mice, which was characterized by a decreased performance on an accelerating rotarod, and that the phenotypic parameters of the transgenic mice were evaluated in controlled studies, which are well-established as tests of locomotor coordination, agility and balance.

This is not found to be persuasive. In reviewing Applicants' data upon which the phenotype of the mice was determined, it is noted that the ranges (i.e., value column) in Table 1 overlap. For example, the first wild-type mouse has a value of 5.96, whereas the last wild-type mouse has a value of 11.42. The knockout mice have values that range in between the values of the two wild-type mice. Thus, the

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Applicants' assertion that there was a "statistically significant difference between the mutants and wild-type mice" (p. 55, lines 22-23), does not to be statistically significant. Further, it appears that, at the very most, 6 wild-type and 6 knockout mice were compared, which does not appear to provide sufficient data to support that the phenotype claimed is statistically significant. Further, it is reiterated that Applicants have failed to provide sufficient guidance or teachings with regard to a specific correlation between the disruption of the chemokine receptor 9A sequence and the claimed phenotype.

Applicants argue that it is generally art-accepted that transgenic mice, such as those claimed by the instant application, represent a valuable tool for determining the function of genes in various conditions or disorders. Thus, Applicants argue that it is generally accepted that gene function is related to and representative of that of human, and that is why the mice provide such a valuable tool. Further, Applicants argue that the instant knockout mice represent a model for the role and function of the chemokine receptor 9A gene. The phenotype of the transgenic mice shows that the gene plays a role in agility, coordination and balance, and that knockout of the gene results in decreased agility or coordination or balance. Thus, Applicants argue that the value of such an *in vivo* model of chemokine receptor 9A gene function would be immediately recognized by one of skill in the art. See pp. 5-6 of the Response.

This is not persuasive. Firstly, the uses that Applicants have claimed (determining the function of genes in various conditions or disorders, or using the mice to discover, examine and/or develop potential treatments, for example) are not specific utilities and are generally applicable to any transgenic mouse. Further, Applicants' argument that it is art-recognized to knockout a gene in a mouse to determine the function of genes in various conditions or disorders constitutes conducting further research to functionally characterize the gene. Thus, the need for such research clearly indicates that gene and its function and correlation to a specific disease is not disclosed as a currently available or substantial utility. Thus, the research contemplated by Applicants, to use the claimed mice to determine the function of gene(s) in various conditions or disorders does not constitute a specific and substantial utility. Identifying and studying the properties of the gene in the context of the knockout mouse does not define a "real world" context or use. Similarly, other asserted utilities that Applicants claim in the instant specification are neither substantial nor specific, due to being generic in nature and applicable to any transgenic knockout mouse.

Applicants further argue that Crabbe (cited in the prior Office action, mailed 5/7/03) fails to establish that phenotypic differences between transgenic knockout mice and a wild-type control mouse, such as those described in the instant specification, are not real and a result of the disruption of the target gene. Particularly, Applicants argue that the Crabbe reference only compares one null

mutant strain to inbred wild-type strains, and this is not representative of a comparison of all knockout mutant mice and their wild-type control counterparts. Further, Applicants argue that the number of mice was tested was low, and thus, statistical assessment of reliability infeasible, and that the results from the Crabbe study can be interpreted in different ways. Thus, Applicants conclude that the Crabbe reference should not broadly be interpreted to apply to all behavioral mouse studies, as Crabbe fails to describe any problems in consistency between labs demonstrated for the rotarod test, used in the instant specification. Applicants argue that the instant specification compares +/- mice with +/+ mice in a controlled laboratory setting, and thus, the results would be accepted by the skilled artisan as demonstrating a role for the chemokine receptor 9A gene and motor related disorders.

This is not persuasive. As stated *supra*, the evidence of record has not provide any correlation between decreased agility/coordination or balance and any disease or disorder. Thus, the evidence of record has not provided any other tuiltieis for the claimed transgenic mice which are specific, substantial and credible. Furthermore, as stated previously, the data provided by the instant specification is such that it is unclear that the results are statistically significant. Although Crabbe does not specifically address the rotarod test, they do show that the behavioral phenotype of mice is dependent upon the laboratory environment, as well as the genetic background of mice. This is supported by the art, for example

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Rustay *et al.* [PNAS, 100(5):2917-2922 (2003)], state that, "Studies of inbred strains, selected lines and transgenic animals have shown that rotarod performance is highly influenced by genetic background in mice." See p. 2917, 1st column, 1st ¶. With particular regard to the rotarod, they state, "Although the rotarod is widely used in biomedical research, there is little consensus on the ideal parameters and test schedules to produce optimal results." p. 2917, 1st column, 2nd ¶. They further state that specific genotypes may perform well under certain test conditions and poorly under others, and provide the example of knockout serotonin 1B receptor subtype mice which were less sensitive to ethanol than the 129 wild-type when using two assays of intoxication, but do not differ in sensitivity when using other behavioral assays, including the accelerating rotarod. See p. 2917, col. 1-2, bridging ¶. They further provide evidence showing that in wild-type mice, difference strains of mice perform in varying ways on the accelerating rotarod. They conclude the following:

Our data show the sensitivity of behavioral genetic results to specifics of the apparatus and protocol, and underscore the importance of adopting test parameters appropriate for a given experimental question. Further, they imply that more than a single test variant is required to characterize a complex behavioral domain, such as ataxia. Single variants of the rotarod task are often used to characterize targeted mutants, but such findings may not generalize widely. Systematic work with several genotypes and multiple tasks, each capturing different parts of the behavioral domain, will be necessary to understand the paths from behavioral assays through their component traits and biological substrates to specific genes. See p. 2922, 2nd column, last ¶.

Although Applicants argue that the claimed phenotypes are specific to the claimed mouse, it is reiterated that a phenotype specific to the mouse does not render the utility of the mouse specific. The claimed phenotypes are not specific to any disease or disorder such that there would be a specific use for the mice.

Thus, it is maintained that neither specification, nor the art of record provides evidence of the existence of a correlation between decreased agility, coordination or balance and a disease or disorder, leaving the skilled artisan to speculate and investigate the uses of the transgenic mouse encompassed by the claims. The specification essentially provides an invitation to experiment, wherein the artisan is invited to elaborate a functional use for the transgenic mouse encompassed by the claim. Thus, the skilled artisan would not find the asserted utility of the claimed transgenic mice to be specific and substantial.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 31-39 are also rejected under 35 U.S.C. 112, first paragraph.

Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112

The prior rejection of claims 38 and 39 is withdrawn in view of Applicants' amendment to the claim to recite "mouse".

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Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Amy Nelson, Acting SPE of Art Unit 1632, at (571) 272-0804. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

twt

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